Journal of Computational and Applied Mathematics 236 (2012) 3572–3583

Contents lists available at SciVerse ScienceDirect

Journal of Computational and Applied Mathematics

journal homepage: www.elsevier.com/locate/cam

Analytics and numerics of drug release tracking☆

José Augusto Ferreira [a,*], Paula de Oliveira [a], Pascoal da Silva [b]

[a] CMUC, Department of Mathematics, University of Coimbra, 3001-454, Coimbra, Portugal

[b] Department of Physics and Mathematics, ISEC, Rua Pedro Nunes, Quinta da Nora, 3030-199 Coimbra, Portugal

ARTICLE INFO

Article history:
Received 30 September 2010
Received in revised form 14 April 2011

Keywords:
Integro-differential equation
Viscoelasticity
Qualitative properties
Numerical methods

ABSTRACT

The study of the dependence of fluxes, concentrations and response times, on the characteristic properties of drug delivery polymeric devices, plays an important role in the design of drug release platforms. The aim of this paper is to develop mathematical tools for an in-depth understanding of drug release tracking. The mathematical model presented takes into account the viscoelastic properties of the polymer and the state of the dispersed drug: free or chemically bound to the matrix. For nonlinear chemical bounds the process is described by a nonlinear integro-differential system and the drug release tracking is treated numerically. For linear chemical bounds closed formulas for the fluxes and response times are established in terms of the parameters that characterize the drug and the platform. These formulas provide a set of a priori estimations for the variables of the model. Numerical examples which show the effectiveness of the approach are included.

1. Introduction

Let us consider the system of partial differential equations

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + E\frac{\partial^2 \sigma}{\partial x^2} + f(u, v) \quad \text{in } (-\ell, \ell) \times (0, T], \tag{1}$$

$$\frac{\partial v}{\partial t} = g(u, v) \quad \text{in } (-\ell, \ell) \times (0, T], \tag{2}$$

$$\frac{\partial \sigma}{\partial t} + \beta\sigma = \alpha u + \gamma\frac{\partial u}{\partial t} \quad \text{in } (-\ell, \ell) \times (0, T]. \tag{3}$$

System (1)–(3) can be used to model drug delivery from a homogeneous polymeric membrane with length 2ℓ. In this case and assuming that inside of the membrane we have only one drug specie, u, v represent the concentration of the drug in two different states. For example the drug can be freely dispersed in the polymeric membrane but also chemically bound to the polymeric matrix (see [1] when the viscoelastic effect is not considered). Another example occurs when the drug is free but also entrapped in nanoparticles dispersed in the polymeric membrane (see [2] when the viscoelastic effect is not considered). In this case u, v denote the concentrations of the free and entrapped drug, respectively. The reaction terms f and g represent the physical and chemical processes involved in the delivery process. In the previous examples they can represent binding or the transference from the particles to the matrix. The viscoelastic behavior of the polymeric matrix is described by (3) where σ represents the stress [3–6]. We note that different viscoelastic models, such as the Maxwell or

☆ This work was partially supported by Projects: PTDC/MAT/74548/2006, UTAustin/MAT/0066/2008.

* Corresponding author.
E-mail address: ferreira@mat.uc.pt (J.A. Ferreira).

0377-0427/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.cam.2011.04.023

Maxwell–Voigt models [7,8], can be obtained as a particular case of (3). In (1)–(3), D stands for the diffusion coefficient of the drug in the polymer, α, β and γ are positive parameters that characterize the mechanical behavior of the material and E "weights" the influence of the non-Fickian flux. We postpone for Section 2 some comments on the sign of E. We note that in [8,4,5], the relaxation time $\frac{1}{\beta}$ is a function of the concentration. However when working in a regime where the polymer is either in the rubbery or the glassy state β is nearly invariant within the states. Moreover this condition is essential to allow analytical manipulation within the framework of Laplace transforms and to simplify the analysis in Section 2.1.

The characterization of the drug delivery device, that is the selection of the parameters that define the polymeric matrix, depend on the requirements previously imposed by medical specifications namely a therapeutical drug flux or a total mass released at specific times. The dependence on the parameters of such flux (or released mass) and the time to attain it, have an important role in the design of the device. For the general nonlinear models (1)–(3) this dependence can only be studied numerically. This fact motivates the study of the qualitative properties of system (1)–(3) as well as the establishment of a class of numerical methods that mimic this differential model.

For linear reactions f and g, a priori estimations for the flux or total mass released, at a certain time t, can be obtained. Particular attention will be given to functions of type $f(u, v) = -K_b u + K_\mu v$, $g(u, v) = -f(u, v)$. In this case, (1)–(3) can be used to model the drug delivery with binding of drug to immobilizing sites and release from these sites as well drug delivery when loaded particles are used to entrap the drug. The theory of Laplace transforms is used to obtain such estimations which are given by closed formulas exhibiting an explicit dependence on the parameters that characterize the drug and the delivery device. The theoretical concept that underlies the approach is the effective time [9], a time constant that gives a priori information about the time when the delivery process can be regarded as completed to some specific extent.

This paper is organized as follows. Section 2 is devoted to the study of system (1)–(3) when natural boundary conditions are imposed. Energy estimates for this problem will be established and a numerical method that mimics the properties of the initial problem is introduced. Using this method we illustrate the behavior of the concentrations u and v, the flux at a specified boundary and the released mass as well. An estimation of the time needed to attain specified levels is also computed. The linearized version of (1)–(3) is studied in Section 3 for Dirichlet boundary conditions and natural boundary conditions. Explicit formulas for the fluxes (or masses) and response times are established in terms of the parameters that characterize the drug and the platform.

2. A nonlinear integro-differential model

We start by rewriting the differential system (1)–(3) as an equivalent integro-differential system. From (3) we have

$$\sigma(x, t) = \mathrm{e}^{-\beta t}\sigma(x, 0) + (\alpha - \beta\gamma)\int_0^t \mathrm{e}^{-\beta(t-s)}u(x, s)\mathrm{d}s + \gamma u(x, t) - \gamma u(x, 0)\mathrm{e}^{-\beta t}. \tag{4}$$

Assuming that the initial stress $\sigma(x, 0)$ and the initial concentration $u(x, 0)$ are constant, we deduce from (1)

$$\frac{\partial u}{\partial t} = D^*\frac{\partial^2 u}{\partial x^2} + E^*\int_0^t \mathrm{e}^{-\beta(t-s)}\frac{\partial^2 u}{\partial x^2}(s)\mathrm{d}s + f(u, v) \quad \text{in}(0, \ell)\times(0, T], \tag{5}$$

which replaces in our mathematical models Eqs. (1) and (3). In Eq. (5) $D^* = D + E\gamma$ and $E^* = E(\alpha - \beta\gamma)$. We remark that Eq. (5) admits the representation

$$\frac{\partial u}{\partial t} + \frac{\partial J}{\partial x} = f(u, v), \tag{6}$$

where J is the non-Fickian flux defined by

$$J(x, t) = -D^*\frac{\partial u}{\partial x}(x, t) - E^*\int_0^t \mathrm{e}^{-\beta(t-s)}\frac{\partial u}{\partial x}(x, s)\mathrm{d}s. \tag{7}$$

The first term on the right-hand side of (7) represents a Fickian flux with diffusion coefficient D^*, with $D^* = D + E\gamma$; the second term stands for a viscoelastic contribution, with weight E^*, where $E^* = E(\alpha - \gamma\beta)$. Following [10,11], the coefficient E is negative, which reflects a certain opposition of the polymeric structure to the Fickian diffusion. In this case $D + E\gamma < D$, and the positivity of D^* must be ensured. The sign of E^* depends on the value $\alpha - \gamma\beta$. For Maxwell and Maxwell–Voigt models, $E^* > 0$ [12]. For the viscoelastic model in [10], $E^* < 0$, which corresponds to a flux overshoot. However we note that in [8] E is considered positive. The fact that different assumptions on the sign of E can be found in the literature is a result of the huge variety of behaviors presented by polymeric matrices. In the approach followed in the present paper, E can be considered positive or negative provided that $D^* > 0$ and $E^* > 0$.

The mathematical models (2) and (5) is coupled with the boundary conditions

$$J(-\ell, t) = \mu_1(u_{\text{ext}} - u(-\ell, t)), \qquad -J(\ell, t) = \mu_2(u_{\text{ext}} - u(\ell, t)), \quad t \in (0, T], \tag{8}$$

and with the initial conditions

$$u(x, 0) = u_0, \qquad v(x, 0) = v_0, \quad x \in (-\ell, \ell). \tag{9}$$

In (8) $\mu_i \geq 0$, $i = 1, 2$, and u_{ext} stands for the an external drug concentration.

In Section 2.1 we present some qualitative properties of the mathematical models (2), (5), (8) and (9). A numerical method that mimics the continuous model is studied in Section 2.2. We point out that numerical methods for integro-differential equations have been proposed in the literature. Without being exhaustive we mention [13–21].

2.1. Energy estimates

We denote by $L^2(0,T,V)$, where $V = H^1(-\ell,\ell)$ or $V = L^2(-\ell,\ell)$, the space of functions p defined in $(-\ell,\ell)\times[0,T]$ and such that, $p(t)\in V$ and $\int_0^T \|p(t)\|_V^2\,\mathrm{d}t < \infty$. Let $(u,v)\in L^2(0,T,H^1(-\ell,\ell))\times L^2(0,T,L^2(-\ell,\ell))$ be a solution of the following system

$$\begin{aligned}\left(\frac{\partial u}{\partial t}(t),u_1\right) &= -\left(D^*\frac{\partial u}{\partial x}(t),u_1'\right) - E^*\int_0^t \mathrm{e}^{-\beta(t-s)}\left(\frac{\partial u}{\partial x}(s),u_1'\right)\mathrm{d}s + (f(u(t),v(t)),u_1)\\ &\quad + \mu_1(u_{\mathrm{ext}}-u(-\ell,t))u_1(-\ell) + \mu_2(u_{\mathrm{ext}}-u(\ell,t))u_1(\ell),\quad \forall u_1\in H^1(-\ell,\ell),\end{aligned} \tag{10}$$

$$\left(\frac{\partial v}{\partial t}(t),v_1\right) = (g(u(t),v(t)),v_1),\quad \forall v_1\in L^2(-\ell,\ell), \tag{11}$$

where $(.,.)$ denotes the usual inner product in $L^2(-\ell,\ell)$.

As this section is devoted to the stability analysis of the IBVP (9), (10), (11), with respect to perturbations of the initial conditions we assume without loss of generality that $u_{\mathrm{ext}} = 0$. We establish in what follows an estimation for

$$E_{\mathrm{grad}}(t) = M_{\mathrm{tot}}(t) + 2D^*\int_0^t\left\|\frac{\partial u}{\partial x}(s)\right\|^2\mathrm{d}s + E^*\left\|\int_0^t \mathrm{e}^{-\beta(t-s)}\frac{\partial u}{\partial x}(s)\mathrm{d}s\right\|^2,\quad t\in[0,T],$$

where $M_{\mathrm{tot}}(t) = \|u(t)\|^2 + \|v(t)\|^2$ and $\|.\|$ represents the norm induced by the inner product $(.,.)$.

It is physically reasonable to assume that the reaction rates of f and g with respect to the concentrations u and v as well as the concentrations u and v are bounded. As f and g are defined in a certain domain $[c,d]\times[c,d]$, we assume mathematically the following assumptions:

$$u(x,t),\,v(x,t)\in[c,d],\ (x,t)\in[-\ell,\ell]\times[0,T],\quad f(0,0) = g(0,0) = 0,\ f,g\in C^1([c,d]\times[c,d]). \tag{12}$$

We use the notations: $f_{u,\max} = \max_{[c,d]\times[c,d]}\frac{\partial f}{\partial u}$, $|f_{v,\max}| = \max_{[c,d]\times[c,d]}|\frac{\partial f}{\partial v}|$, $|g_{u,\max}| = \max_{[c,d]\times[c,d]}|\frac{\partial g}{\partial u}|$ and $g_{v,\max} = \max_{[c,d]\times[c,d]}\frac{\partial g}{\partial v}$.

Theorem 1. *Let $(u,v)\in L^2(0,T,H^1(-\ell,\ell))\times L^2(0,T,L^2(-\ell,\ell))$ be a solution of the variational problems (10), (11) with initial condition (9). If (12) holds then*

$$E_{\mathrm{grad}}(t)\le \mathrm{e}^{\max\{0,\Phi\}t}M_{\mathrm{tot}}(0), \tag{13}$$

where

$$\Phi = 2\max\left\{f_{u,\max} + \epsilon^2(|f_{v,\max}| + |g_{u,\max}|), g_{v,\max} + \frac{1}{4\epsilon^2}(|f_{v,\max}| + |g_{u,\max}|)\right\} \tag{14}$$

and $\epsilon\neq 0$ is an arbitrary constant.

Proof. Taking in (10), (11), $u_1 = u(t)$ and $v_1 = v(t)$, respectively, we easily obtain

$$\begin{aligned}\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\|u(t)\|^2 &= -D^*\left\|\frac{\partial u}{\partial x}(t)\right\|^2 - E^*\int_0^t \mathrm{e}^{-\beta(t-s)}\left(\frac{\partial u}{\partial x}(s),\frac{\partial u}{\partial x}(t)\right)\mathrm{d}s\\ &\quad - \mu_1 u(0,t)^2 - \mu_2 u(\ell,t)^2 + (f(u(t),v(t)),u(t)),\end{aligned} \tag{15}$$

and

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\|v(t)\|^2 = (g(u(t),v(t)),v(t)).$$

Let us consider now $(f(u(t),v(t)),u(t))$. We have

$$\begin{aligned}(f(u(t),v(t)),u(t)) &= \left(f(0,0) + \frac{\partial f}{\partial u}(\theta_1 u(t),v(t))u(t) + \frac{\partial f}{\partial v}(0,\theta_2 v(t))v(t),u(t)\right)\\ &\le f_{u,\max}\|u(t)\|^2 + |f_{v,\max}||(u(t),v(t))|,\end{aligned}$$

where $\theta_1,\theta_2\in[0,1]$. Analogously, it can be shown that

$$(g(u(t),v(t)),v(t))\le g_{v,\max}\|v(t)\|^2 + |g_{u,\max}||(u(t),v(t))|.$$

Consequently

$$\begin{aligned}&(f(u(t),v(t)),u(t))+(g(u(t),v(t)),v(t))\\&\quad\le f_{u,\max}\|u(t)\|^2+g_{v,\max}\|v(t)\|^2+(|f_{v,\max}|+|g_{u,\max}|)|(u(t),v(t))|\\&\quad\le (f_{u,\max}+\epsilon^2(|f_{v,\max}|+|g_{u,\max}|))\|u(t)\|^2+\left(g_{v,\max}+\frac{1}{4\epsilon^2}(|f_{v,\max}|+|g_{u,\max}|)\right)\|v(t)\|^2,\end{aligned}$$

where $\epsilon\neq 0$ is an arbitrary constant. As

$$\int_0^t \mathrm{e}^{-\beta(t-s)}\left(\frac{\partial u}{\partial x}(s),\frac{\partial u}{\partial x}u(t)\right)\mathrm{d}s=\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\left\|\int_0^t \mathrm{e}^{-\beta(t-s)}\frac{\partial u}{\partial x}(s)\mathrm{d}s\right\|^2+\beta\left\|\int_0^t \mathrm{e}^{-\beta(t-s)}\frac{\partial u}{\partial x}(s)\mathrm{d}s\right\|^2,$$

we deduce

$$\begin{aligned}&\frac{\mathrm{d}}{\mathrm{d}t}\left(M_{\mathrm{tot}}(t)+2D^*\int_0^t\left\|\frac{\partial u}{\partial x}(s)\right\|^2\mathrm{d}s+E^*\left\|\int_0^t \mathrm{e}^{-\beta(t-s)}\frac{\partial u}{\partial x}(s)\mathrm{d}s\right\|^2\right)\\&\quad\le -2\beta E^*\left\|\int_0^t \mathrm{e}^{-\beta(t-s)}\frac{\partial u}{\partial x}(s)\mathrm{d}s\right\|^2+\Phi M_{\mathrm{tot}}(t),\end{aligned}\tag{16}$$

where Φ is defined by (14).

Finally, applying the Gronwall lemma to inequality (16) we obtain (13). □

Let us analyze the meaning of estimation (13). If $\Phi\le 0$ then $E_{\mathrm{grad}}(t)\le E_{\mathrm{grad}}(0)$ for all $t\in[0,+\infty)$. Otherwise $E_{\mathrm{grad}}(t)$ is bounded in bounded time intervals. Estimation (13) does not allow us to conclude the convergence to zero of $\|u(t)\|$, $\|v(t)\|$ and $\frac{\partial u}{\partial x}$. Nevertheless, if in (15) we do not consider the term $-D^*\left\|\frac{\partial u}{\partial x}(t)\right\|$ we obtain

$$\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\|u(t)\|^2\le -E^*\int_0^t \mathrm{e}^{-\beta(t-s)}\left(\frac{\partial u}{\partial x}(s),\frac{\partial u}{\partial x}(t)\right)\mathrm{d}s-\mu_1u(-\ell,t)^2-\mu_2u(\ell,t)^2+(f(u(t),v(t)),u(t)),\tag{17}$$

which is used to prove Theorem 2 where we establish an estimation for

$$E_{\mathrm{int}}(t)=M_{\mathrm{tot}}(t)+E^*\left\|\int_0^t \mathrm{e}^{-\beta(t-s)}\frac{\partial u}{\partial x}(s)\mathrm{d}s\right\|^2.$$

Theorem 2. *Let $(u,v)\in L^2(0,T,H^1(-\ell,\ell))\times L^2(0,T,L^2(-\ell,\ell))$ be a solution of the variational problems (10), (11) with initial condition (9). If (12) holds then*

$$E_{\mathrm{int}}(t)\le \mathrm{e}^{\max\{-2\beta,\Phi\}t}M_{\mathrm{tot}}(0),\tag{18}$$

where Φ is defined by (14). □

If the reaction terms f and g are such that $\Phi<0$, then from the last result we obtain

$$\|u(t)\|^2+\|v(t)\|^2+E^*\left\|\int_0^t \mathrm{e}^{-\beta(t-s)}\frac{\partial u}{\partial x}(s)\mathrm{d}s\right\|^2\to 0,\quad t\to+\infty.\tag{19}$$

We take $\epsilon=\frac{1}{\sqrt{2}}$. Then for f and g such that

$$f_{u,\max}<-\frac{1}{2}(|f_{v,\max}|+|g_{u,\max}|)\quad\text{and}\quad g_{v,\max}\le-\frac{1}{2}(|f_{v,\max}|+|g_{u,\max}|),\tag{20}$$

the convergence (19) holds. This condition means that in (1) and (2), the reaction rates of f and g with respect to the concentrations, respectively, u and v are negative and less than the average of the absolute values of the reaction rates of f and g with respect to the concentrations, respectively, v and u.

We particularize Theorem 2 for the linear case considered in [1] when the viscoelastic effect is not considered. In this case u and v represent, respectively, the free and bound concentration specie, $f(u,v)=-(K_u+r_u)u+K_vv$, $g(u,v)=k_uu-(K_v+r_v)v$, where K_u and K_v represent, respectively, the reaction rates of bound and unbound concentrations and r_u and r_v represent, respectively, first-order elimination rates for free and bound concentrations. Condition (20) is equivalent to

$$r_u>\frac{1}{2}(K_v-K_u),\qquad r_v>\frac{1}{2}(K_u-K_v),\tag{21}$$

which establish a lower bound for the degradation rates of both concentrations. Assuming that the degradation rates r_u and r_v satisfy (21) we conclude the convergence (19).

2.2. A discrete model

In this section we present a numerical method to compute an approximation to the solution of (2), (5), (8), (9). The method mimics the continuous model in the sense that it presents the qualitative properties of the continuous model and discrete versions of the results in Theorems 1 and 2 can be established.

In $[-\ell, \ell]$ and $[0, T]$ we introduce, respectively, the following grids

$$I_h = \{x_i, i = 0, \ldots, N, x_0 = -\ell, x_N = \ell, x_i - x_{i-1} = h, i = 1, \ldots, N\},$$
$$\{t_n, t_0 = 0, t_M = T, t_n - t_{n-1} = \Delta t, n = 1, \ldots, M\}.$$

We denote by $W_h(I_h)$ the space of grid functions defined in I_h. We use, for $r_h, p_h \in W_h(I_h)$ the following notations:

$$(r_h, p_h)_{I_h'} = \sum_{i=1}^{N-1} h r_h(x_i) p_h(x_i), \qquad (r_h, p_h)_+ = \sum_{i=1}^{N} h r_h(x_i) p_h(x_i), \qquad \|r_h\|_+^2 = (r_h, r_h)_+,$$

where $I_h' = I_h - \{-\ell, \ell\}$. We also consider the backward finite difference operators D_{-x} and the second-order finite difference operator, respectively,

$$D_{-x} p_h(x_i) = \frac{1}{h}(p_h(x_i) - p_h(x_{i-1})), \quad i = 1, \ldots, N,$$
$$D_2 p_h(x_i) = \frac{1}{h^2}(p_h(x_{i+1}) - 2p_h(x_i) + p_h(x_{i-1})), \quad i = 1, \ldots, N-1.$$

We remark that the following identity holds

$$(D_2 p_h, r_h)_{I_h'} = -(D_{-x} p_h, D_{-x} r_h)_+ - D_{-x} p_h(x_1) r_h(x_0) + D_{-x} p_h(x_N) r_h(x_N). \tag{22}$$

Let $u_h^n \in W_h(I_h)$ and $v_h^n \in W_h(I_h')$ be defined by the following variational problem

$$\begin{aligned}(u_h^{n+1}, u_{1,h})_{I_h'} = {} & (u_h^n, u_{1,h})_{I_h'} - \Delta t D^*(D_{-x} u_h^{n+1}, D_{-x} u_{1,h})_+ \\ & - \Delta t^2 E^* \sum_{j=1}^{n+1} \mathrm{e}^{-\beta(t_{n+1}-t_j)}(D_{-x} u_h^j, D_{-x} u_{1,h})_+ \Delta t (f(u_h^{n+1}, v_h^{n+1}), u_{1,h})_{I_h'} \\ & + \Delta t \mu_1 (u_{\text{ext}} - u_h^{n+1}(x_0)) u_{1,h}(x_0) + \Delta t \mu_2 (u_{\text{ext}} - u_h^{n+1}(x_N)) u_{1,h}(x_N), \quad \forall u_{1,h} \in W_h(I_h),\end{aligned} \tag{23}$$

$$(v_h^{n+1}, v_{1,h})_{I_h'} = (v_h^n, v_{1,h})_{I_h'} + \Delta t (g(u_h^{n+1}, v_h^{n+1}), v_{1,h}), \quad \forall v_{1,h} \in W_H(I_h'), \tag{24}$$

complemented with the initial conditions

$$u_h^0 = u_0 \quad \text{in } I_h, \; v_h^0 = v_0 \text{ in } I_h'. \tag{25}$$

The discrete variational identities (23) and (24) can be seen as discrete versions of the correspondent variational identities (10) and (11). We show in what follows that they are equivalent to a standard finite difference discretization of the partial differential equations (5), (2), respectively. Using identity (22), it can be shown that (23) is equivalent to

$$\begin{aligned}(u_h^{n+1}, u_{1,h})_{I_h'} = {} & (u_h^n, u_{1,h})_{I_h'} + \Delta t D^*(D_2 u_h^{n+1}, u_{1,h})_{I_h'} + \Delta t^2 E^* \sum_{j=1}^{n+1} \mathrm{e}^{-\beta(t_{n+1}-t_j)}(D_2 u_h^j, u_{1,h})_{I_h'} \\ & + \Delta t \left(D^* D_{-x} u_h^{n+1}(x_1) + \Delta t E^* \sum_{j=1}^{n+1} \mathrm{e}^{-\beta(t_{n+1}-t_j)} D_{-x} u_h^j(x_1) \right) u_{1,h}(x_0) \\ & - \Delta t \left(D^* D_{-x} u_h^{n+1}(x_N) + \Delta t E^* \sum_{j=1}^{n+1} \mathrm{e}^{-\beta(t_{n+1}-t_j)} D_{-x} u_h^j(x_N) \right) u_{1,h}(x_N) \\ & + \Delta t \mu_1 (u_{\text{ext}} - u_h^{n+1}(x_0)) u_{1,h}(x_0) + \Delta t \mu_2 (u_{\text{ext}} - u_h^{n+1}(x_N, t)) u_{1,h}(x_N) \\ & + \Delta t (f(u_h^{n+1}, v_h^{n+1}), u_{1,h})_{I_h'} \forall u_{1,h} \in W_h(I_h).\end{aligned}$$

Considering, for each grid point x_i, a grid function $u_{1,h}$ such that $u_{1,h}(x_i) = 1$ and $u_{1,h}(x_j) = 0, j \neq i$, we conclude that

$$\frac{u_h^{n+1} - u_h^n}{\Delta t} = D^* D_2 u_h^{n+1} + E^* \Delta t \sum_{j=0}^{n+1} \mathrm{e}^{-\beta(t_{n+1}-t_j)} D_2 u_h^j + f(u_h^{n+1}, v_h^{n+1}, w_h^{n+1}), \tag{26}$$

and

$$\begin{aligned} &-D^*D_{-x}u_h^{n+1}(x_1) - E^*\Delta t\sum_{j=1}^{n+1} \mathrm{e}^{-\beta(t_{n+1}-t_j)}D_{-x}u_h^j(x_1) = \mu_1(u_{\mathrm{ext}} - u_h^{n+1}(x_0)),\\ &D^*D_{-x}u_h^{n+1}(x_N) + E^*\Delta t\sum_{j=1}^{n+1} \mathrm{e}^{-\beta(t_{n+1}-t_j)}D_{-x}u_h^j(x_N) = \mu_2(u_{\mathrm{ext}} - u_h^{n+1}(x_N)). \end{aligned} \tag{27}$$

From (26) and from the boundary conditions (27) we conclude that (23) holds. Analogously, it can be shown that (24) is equivalent to

$$\frac{v_h^{n+1} - v_h^n}{\Delta t} = g(u_h^{n+1}, v_h^{n+1}). \tag{28}$$

Consequently, to compute the solution of the discrete variational problems (23), (24), with the initial condition (25) is equivalent to solving the finite difference equations (26), (28) coupled with conditions (25), (27).

In the next result an estimation for

$$E_{\mathrm{int},h}(t_n) = M_{\mathrm{tot},h}(t_n) + E^*\left\|\Delta t\sum_{j=1}^{n} \mathrm{e}^{-\beta(t_n-t_j)}D_{-x}u_h^j\right\|_+^2, \quad n = 1,\ldots,M,$$

is established. In the definition of $E_{\mathrm{int},h}(t_n)$ we used the notation $M_{\mathrm{tot},h}(t_n) = \|u_h^n\|_{I_h'}^2 + \|v_h^n\|_{I_h'}^2$. We remark that as $E_{\mathrm{int},h}(t_n)$ is a discrete version of $E_{\mathrm{int}}(t_n)$, Theorem 3 can be seen as a discrete version of Theorem 2 and we need to assume a discrete version of the assumptions (12)

$$u_h^n(x_i), v_h^n(x_i) \in [c,d], \quad i = 1,\ldots,N-1,\ n = 1,\ldots,M,\ f(0,0) = g(0,0) = 0,\ f,g \in C^1([c,d]\times[c,d]). \tag{29}$$

Theorem 3. *Let $u_h^n \in W_h(I_h)$, $v_h^n \in W_h(I_h')$, $n = 1,\ldots,M$, be defined by (26), (28), coupled with conditions (25), (27), with $u_{\mathrm{ext}} = 0$ and $E^* > 0$. If (29) holds then*

$$E_{\mathrm{int},h}(t_n) \le \frac{1}{\min\{1-2\Delta t\Phi,\,1\}^n}M_{\mathrm{tot},h}(t_0), \tag{30}$$

for Δt such that

$$1 - 2\Delta t\Phi > 0, \tag{31}$$

where Φ is defined by (14).

Proof. Considering in (23) and (24) $u_{1,h} = u_h^{n+1}$, $v_{1,h} = v_h^{n+1}$, respectively, and using the Cauchy–Schwarz inequality we obtain

$$\begin{aligned} \frac{1}{2}\|u_h^{n+1}\|_{I_h'}^2 \le{}& \frac{1}{2}\|u_h^n\|_{I_h'}^2 - \Delta tD^*\|D_{-x}u_h^{n+1}\|_+^2 - \Delta t^2E^*\sum_{j=1}^{n+1}\mathrm{e}^{-\beta(t_{n+1}-t_j)}(D_{-x}u_h^j, D_{-x}u_h^{n+1})_+\\ &+ \Delta t(f(u_h^{n+1}, v_h^{n+1}), u_h^{n+1})_{I_h'} - \Delta t\mu_1u_h^{n+1}(x_0)^2 - \Delta t\mu_2u_h^{n+1}(x_N) \end{aligned} \tag{32}$$

and

$$\frac{1}{2}\|v_h^{n+1}\|_{I_h'}^2 \le \frac{1}{2}\|v_h^n\|_{I_h'}^2 + \Delta t(g(u_h^{n+1}, v_h^{n+1}), v_h^{n+1})_{I_h'}. \tag{33}$$

As

$$\begin{aligned} \left(\sum_{j=1}^{n+1}\mathrm{e}^{-\beta(t_{n+1}-t_j)}D_{-x}u_h^j, D_{-x}u_h^{n+1}\right)_+ ={}& \frac{1}{2}\left\|\sum_{j=1}^{n+1}\mathrm{e}^{-\beta(t_{n+1}-t_j)}D_{-x}u_h^j\right\|_+^2\\ &- \frac{1}{2}\mathrm{e}^{-2\beta\Delta t}\left\|\sum_{j=1}^{n}\mathrm{e}^{-\beta(t_n-t_j)}D_{-x}u_h^j\right\|_+^2 + \frac{1}{2}\|D_{-x}u_h^{n+1}\|_+^2, \end{aligned}$$

it can be shown, from (32), (33) and following the proof of Theorem 1, that

$$(1-2\Delta t\Phi)M_{\mathrm{tot},h}(t_{n+1}) + E^*\left\|\Delta t\sum_{j=1}^{n+1}\mathrm{e}^{-\beta(t_{n+1}-t_j)}D_{-x}u_h^j\right\|_+^2 \le M_{\mathrm{tot},h}(t_n) + E^*\|\Delta t\sum_{j=1}^{n}\mathrm{e}^{-\beta(t_n-t_j)}D_{-x}u_h^j\|_+^2,$$

that is, $\min\{1-2\Delta t\Phi,\,1\}E_{\mathrm{int},h}(t_{n+1}) \le E_{\mathrm{int},h}(t_n)$.

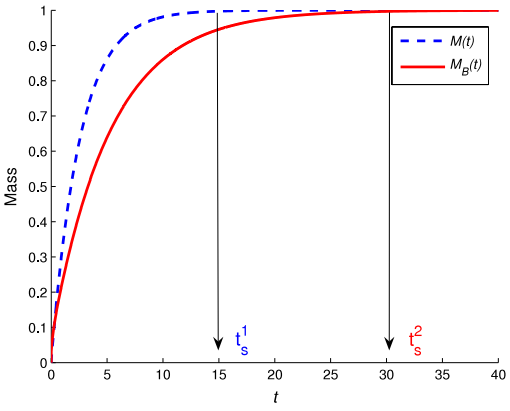

Fig. 1. Numerical released masses computed with the numerical scheme (26), (28), (27): M_B obtained with binding; M obtained without binding.

Table 1
Numerical simulations of the total mass released obtained with $D = 0.6$, $\gamma = 1, \alpha = 0.2$ for M_1 (with $E = -0.2$, $\beta = 1$), M_2 (with $E = -0.59$, $\beta = 1$), and M_3 (with $E = -0.59$, $\beta = 0.25$).

Time	M_1	M_2	M_3
$t_1 = 5.55$	0.6758	0.6728	0.5825
$t_2 = 11.11$	0.8869	0.8858	0.8552
$t_3 = 16.66$	0.9603	0.9599	0.9484
$t_4 = 22.21$	0.9861	0.9859	0.9816
$t_5 = 27.76$	0.9951	0.9950	0.9934

This inequality implies that

$$E_{\text{int},h}(t_{n+1}) \leq \frac{1}{\min\{1 - 2\Delta t\Phi, 1\}^n} E_{\text{int},h}(t_1),$$

provided that Δt satisfies (31). As

$$E_{\text{int},h}(t_1) \leq \frac{1}{\min\{1 - 2\Delta t\Phi, 1\}} M_{\text{tot},h}(t_0),$$

we conclude inequality (30) provided that condition (31) holds. □

As a corollary of Theorem 3 we have the stability result:

Corollary 1. *The finite difference method (26), (28) coupled with the boundary conditions (27) is unconditionally stable provided that $\Phi \leq 0$ and it is conditionally stable for $\Phi > 0$.*

2.3. Numerical results

In this section we illustrate the use of the numerical scheme (26), (28) in the computation of the released mass. We observe that an estimation of the time when the steady state is attained can be obtained from the numerical values of the mass. We take $D = 0.6$, $\gamma = 1$, $\alpha = 0.2$, $E = -0.2$, $\beta = 1$, $\mu_1 = \mu_2 = 0.2$ and $\ell = 0.5$.

In Fig. 1 we plot the numerical mass M_B obtained when binding occurs and is represented by the nonlinear functions $f(u, v) = -u(u + 2) + v(v + 2)$, $g(u, v) = -f(u, v)$. The form of f reflects the fact that in mass balance (1) there is a positive contribution of bound drug which becomes free and a negative contribution of free drug which becomes immobile. In this simulation we used $u_0 = 0.75$, $v_0 = 0.25$. The released mass M when no binding occurs is also represented. To compare both profiles we considered that $u_0 = 1$, in the absence of binding. In the picture t_s^1 and t_s^2 represent the instants when the steady state is attained without and with binding, respectively. We note that, as expected, binding induces a delay in the drug delivery.

In Table 1 we present numerical simulations of the total mass released. The results have been obtained with $D = 0.6$, $\gamma = 1, \alpha = 0.2$ for three different set of parameters: M_1 ($E = -0.2, \beta = 1$), M_2 ($E = -0.59, \beta = 1$), and M_3 ($E = -0.59, \beta = 0.25$). The decreasing of E leads to a delay in the delivery because such a decrease means an increase in the viscoelastic effect. The decreasing of β also leads to a delay in the delivery. In fact when β decreases the relaxation parameter increases which explains the observed delay.

3. Analysis of a linearized drug delivery model

In this section we consider a linear version of the mathematical models (1)–(3). We suppose that $f(u, v) = -K_b u + K_\mu v$ and $g(u, v) = -f(u, v)$, where K_b and K_μ represent rate constants associated respectively with binding of drug to immobilizing sites and release of drug from these sites. We recall that, in the previous context, Eq. (2) can describe binding or transference from loaded microparticles dispersed in the membrane. In fact, if $K_b \neq K_\mu$ system (1)–(3) describes the behavior of drug diffusion through a viscoelastic membrane where binding and unbinding occur but at different rates. If $K_b = K_\mu$, the system represents either diffusion through a viscoelastic membrane with equal rates of binding and unbinding or alternatively the coupling of a drug diffusion with transference from loaded microparticles. We note that in this last case v represents the drug concentration within the microparticles [2].

Proceeding as in Section 2 we easily obtain for u the following integro-differential equation

$$\frac{\partial u}{\partial t} = D^* \frac{\partial^2 u}{\partial x^2} + E^* \int_0^t \mathrm{e}^{-\beta(t-s)} \frac{\partial^2 u}{\partial x^2}(s)\mathrm{d}s + K_\mu K_b \int_0^t \mathrm{e}^{-K_\mu (t-s)} u(s)\mathrm{d}s + K_\mu \mathrm{e}^{-K_\mu t} u(x, 0), \tag{34}$$

where D^* and E^* are defined in Section 2. As we are dealing in this section with a linear equation with constant coefficients, Laplace transforms are well fitted to the analysis. In order to simplify the presentation, we start with Dirichlet boundary conditions and then we consider natural boundary conditions.

3.1. Equilibrium variables and effective time constant

Two important characteristics of drug delivery devices are the steady state flux (or total released mass) and the time required to attain such a state. To compute these characteristics for nonlinear drug delivery models, the problem must be solved numerically. However, if a linear drug delivery model of the type introduced in this section is considered closed formulas for the steady state flux and for the effective time constant can be established without solving analytically the linear problem. From these formulas, estimations for the flux at any time are obtained.

To compute the steady state flux leaving the membrane, the Final Value Theorem of Laplace Transforms can be used. Let $w(x, t)$ represent a state variable. Then this theorem states that $\lim_{t\to\infty} w(x, t) = \lim_{p\to 0} p\overline{w}(x, p)$, where $\overline{w}$ represents the Laplace transform of w, $\overline{w}(x, p) = \int_0^\infty \mathrm{e}^{-pt} w(x, t)\mathrm{d}t$.

From (7), the Laplace transform $\bar{J}(x, p)$ of the flux $J(x, t)$ at $x = \ell$, assumes the form

$$\bar{J}(\ell, p) = -F^* \frac{\partial \overline{u}}{\partial x}(\ell, p), \tag{35}$$

where

$$F^* = \frac{D^*(p + \beta) + E^*}{p + \beta}, \tag{36}$$

and consequently the steady flux $J_s(\ell)$ is given by

$$J_s(\ell) = -\lim_{p\to 0} pF^* \frac{\partial \overline{u}}{\partial x}(\ell, p). \tag{37}$$

As the mass released at time t, at $x = \ell$, $M_\ell(t)$, is defined by $M_\ell(t) = \int_0^t J(\ell, s)\mathrm{d}s$, to compute the equilibrium mass released from the boundary $x = \ell$, $M_s(\ell) = \lim_{t\to+\infty} M_\ell(t)$, we have

$$M_s(\ell) = \lim_{p\to 0} F^* \frac{\partial \overline{u}}{\partial x}(\ell, p). \tag{38}$$

The equilibrium flux (or the equilibrium mass) is given by (37) (or (38)) without solving the integro-differential equation (34) and just by computing the Laplace transform of u. Closed formulas for $J_s(\ell)$ or $M_s(\ell)$, exhibiting explicit dependence on the parameters of the model, will be obtained in Section 3.2 for two different sets of boundary conditions.

We recall now the concept of effective time [9] which is defined as the first moment associated with the density probability function

$$\mathrm{d}(x, t) = \frac{w_s(x) - w(x, t)}{\int_0^\infty (w_s(x) - w(x, t))\mathrm{d}t}, \tag{39}$$

that is

$$t_{\mathrm{eff}}(x) = \frac{\int_0^\infty t(w_s(x) - w(x, t))\mathrm{d}t}{\int_0^\infty (w_s(x) - w(x, t))\mathrm{d}t}, \tag{40}$$

where w represents a state variable and $w_s(x) = \lim_{t\to\infty} w(x, t)$.

As proved in [9], t_{eff} can be computed by

$$t_{\text{eff}}(x) = \lim_{p\to 0} \frac{\frac{w_s(x)}{p} + \frac{\partial \overline{w}}{\partial p}(x,p)}{\frac{w_s(x)}{p} - \overline{w}(x,p)},$$

that is from the Laplace transform of w and without knowing w explicitly. From this last equation it can be established that, if for p small enough, $\overline{w}$ admits the representation

$$\overline{w}(x,p) = -\frac{w_s(x)}{p} + B + Cp + O(p^2), \tag{41}$$

where B and C are p independent, then

$$t_{\text{eff}}(x) = -\frac{C}{B} \tag{42}$$

whenever $B \neq 0$.

Let us suppose that the drug is released at $x = \ell$. A density distribution $d(\ell, t)$ can be computed from $J(\ell, t)$ or $M_\ell(t)$ that is considering in (39) $w(\ell, t) = J(\ell, t)$ or $w(\ell, t) = M(\ell, t)$.

Making the natural ansatz that the density is exponentially shaped, $d(t) = a(t)\mathrm{e}^{-b(t)}$, then as $\int_0^\infty \mathrm{d}(s)\mathrm{d}s = 1$, we have $a(t) = b(t)$ and, from (39), $a(t) = t_{\text{eff}}^{-1}$. With this ansatz, t_{eff} can be viewed as the first moment of the exponential distribution $d^*(t) = \frac{1}{t_{\text{eff}}}\mathrm{e}^{-\frac{t}{t_{\text{eff}}}}$. Consequently, interpreting t as a statistical variable, we have

$$P(t \leq Kt_{\text{eff}}) = 1 - \mathrm{e}^{-K}, \quad \forall K \in \mathbb{R}_0^+, \tag{43}$$

and an estimation $\tilde{w}(\ell, t)$ for $w(\ell, t)$, where $w(\ell, t)$ represents $J(\ell, t)$ or $M_\ell(t)$ can be obtained from

$$\tilde{w}(\ell, Kt_{\text{eff}}) = (1 - \mathrm{e}^{-K})w_s(\ell), \quad \forall K \in \mathbb{R}_0^+. \tag{44}$$

From (44) we note that to compute an estimation for $w(\ell, t)$ at $t = Kt_{\text{eff}}$, only the steady state value $w_s(\ell)$ and the effective time t_{eff} must be known. This approach provides closed analytical formulas for the estimations that can be used not only to give an in-depth understanding of delivery process but also useful quantitative approximations.

3.2. Closed forms for the steady state variables and effective time constant

We compute in what follows the steady state flux (or the total delivered mass) and the effective time for problem (34) with two different sets of boundary conditions.

3.2.1. Dirichlet boundary conditions

Let the membrane occupy $[0, \ell]$ and the boundary conditions be represented by

$$u(0,t) = u_d, \qquad u(\ell,t) = 0, \quad t > 0. \tag{45}$$

The initial conditions are defined by $u(x,0) = v(x,0) = \sigma(x,0) = 0$. The concentration u_d is related to a donor cell concentration at $x = 0$ and at $x = \ell$ a sink condition is applied.

Taking the Laplace transform of (34) and (45) we obtain

$$\bar{u}(x,p) = \frac{u_d \sinh(A(\ell - x))}{p \sinh(A\ell)}, \tag{46}$$

where

$$A^2 = \frac{p(p + K_b + K_\mu)(p + \beta)}{(p + K_\mu)(D^*(p + \beta) + E^*)}. \tag{47}$$

Replacing (46) in (35) and using the Final Value Theorem we obtain $J_s(\ell) = \frac{u_d}{\ell}\frac{\beta D^* + E^*}{\beta}$. We note that the steady flux does not depend on the rates of binding and unbinding and just depends on the viscoelastic properties of the membrane. When no viscoelastic effects are considered, $E^* = 0$, and $J_s(\ell) = \frac{u_d}{\ell}D$ which corresponds to the steady flux of pure Fickian diffusion [22]. We compute the Laplace transform of the flux,

$$\bar{J}(\ell,p) = \frac{u_d}{p\ell}\frac{A}{\sinh(A\ell)}\frac{D^*(p + \beta) + E^*}{p + \beta}, \tag{48}$$

where A is defined in (47). Expanding the hyperbolic function in powers of p we give (48) the form (41), and following (42) we establish closed formulas for t_{eff}.

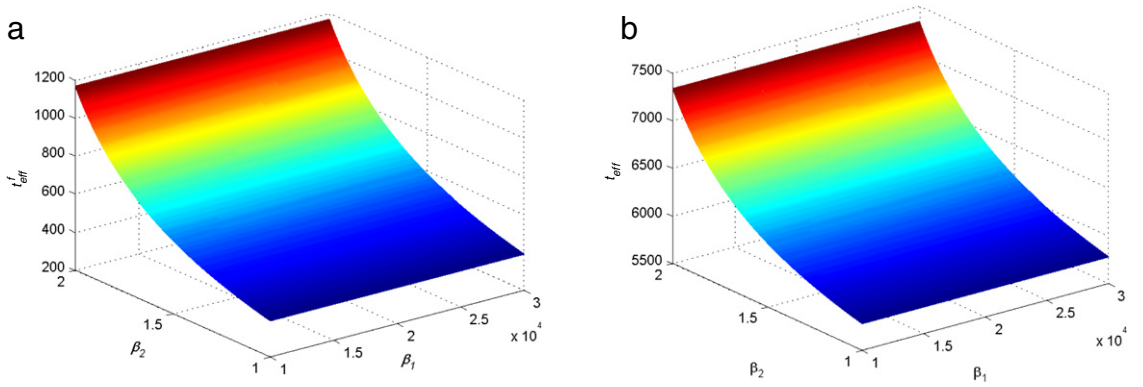

Fig. 2. Behavior of t_{eff}, when t_{eff} is a function of the parameters β_1, β_2,: (a) without binding given by (50); (b) with binding given by (51).

If no viscoelastic effects are considered – Problem I – we obtain, from (42),

$$t_{\text{eff}} = \frac{K_b}{K_\mu(K_\mu + K_b)} + \frac{7}{60}\frac{\ell^2}{D}\left(1 + \frac{K_b}{K_\mu}\right). \tag{49}$$

We note that $\frac{\partial t_{\text{eff}}}{\partial K_b} > 0$, $\frac{\partial t_{\text{eff}}}{\partial K_\mu} < 0$ which represents an expected physical behavior. In fact as the binding rate K_b increases the mean time to attain equilibrium increases and as the unbinding rate K_μ increases, time decreases.

If $K_b = 0$, that is no binding occurs, then the effective time of a pure diffusion problem is obtained. In the case where only viscoelastic effects are considered – Problem II – we obtain

$$t_{\text{eff}} = \frac{1}{D^*\beta + E^*}\left(\frac{E^*}{\beta} + \frac{\beta\ell^2}{3!} + \frac{D^*E^*\ell - \frac{2}{3!}\beta E^*\ell^3 - \frac{1}{5!}\beta^3\ell^5}{E^*\ell + \frac{1}{3!}\beta^2\ell^3}\right). \tag{50}$$

The behavior of effective time (50) has been studied in [12] for different viscoelastic models obtained from (3) with $\beta = \frac{\beta_1+\beta_2}{2}$, $\alpha = \frac{\beta_1\beta_2}{2}$ and $\gamma = \beta_2$, where $\beta_1 + \beta_2$ represents the Young modulus. We mention that t_{eff} increases with the Young modulus as reported by experimentalists in the literature [23,24]. If problems (1)–(3) with $f(u, v) = -K_b u + K_\mu v$ and $g(u, v) = -f(u, v)$ are considered, that is, if diffusion, viscoelasticity and binding occur – Problem III – then following the same procedure we obtain

$$t_{\text{eff}} = \frac{\beta}{\beta D + E\alpha}\left(1 + \frac{K_b}{K_\mu}\right)\frac{7\ell^2}{60} - \frac{1}{\beta} - \frac{1}{K_\mu + K_b} + \frac{D^*K_\mu + \beta D + E\alpha}{K_\mu(\beta D + E\alpha)}. \tag{51}$$

We note that (51) holds for $\beta, K\mu, K_b \neq 0$. The particular cases $\beta = 0$ and $K_\mu = K_b = 0$ must be obtained respectively from (49) and (50). The behavior of (51) is illustrated in Fig. 2(b) and it is qualitatively analogous to the behavior of t_{eff} given by (50) (Fig. 2(a)). However the range of variation of t_{eff} is larger in Fig. 2(b) due to the delay effect induced by binding.

3.2.2. Natural boundary conditions

We consider now the natural boundary conditions (8). In this case the equilibrium flux is zero and the variable of interest is the released mass $M(t) = M_{-\ell}(t) + M_\ell(t)$ with $M_a(t) = \int_0^t J(a, s)\text{d}s$, $a = -\ell, \ell$, where $J(x, t)$ is given by (7) and u is the solution of (34), (8) with $u(x, 0) = u_0$, $v(x, 0) = v_0$.

The same approach of Section 3.2.1 is followed but instead of $J(\ell, t)$ the total mass is used. As we have $\overline{M}(p) = \overline{M}_{-\ell}(p) + \overline{M}_\ell(p)$ and $\overline{M}_a(p) = -\frac{2}{p}\overline{J}(a, p)$, $a = \pm\ell$, we begin by computing $\overline{u}$, solution of the following differential problem

$$-F^*\frac{\partial^2\overline{u}}{\partial x^2} + \frac{p(p + K_\mu + K_b)}{p + K_\mu}\overline{u} = u_0 + \frac{K_\mu}{p + K_\mu}v_0 \tag{52}$$

coupled with the boundary conditions

$$-F^*\frac{\partial\overline{u}}{\partial x}(\ell, p) = \mu_1\left(\frac{u_{\text{ext}}}{p} - \overline{u}(\ell, p)\right), \qquad F^*\frac{\partial\overline{u}}{\partial x}(-\ell, p) = \mu_2\left(\frac{u_{\text{ext}}}{p} - \overline{u}(-\ell, p)\right). \tag{53}$$

The differential problems (52), (53) is obtained by applying Laplace transforms to (8), (34). For $\mu_1 = \mu_2 = \mu$, the following solution is obtained $\overline{u}(x, p) = \mu\left(\frac{u_{\text{ext}}}{p} - S\right)\frac{\cosh(Ax)}{AF^*\sinh(A\ell) + \mu\cosh(A\ell)} + S$, where $S = \frac{u_0(p+K_\mu) + K_\mu v_0}{p(p+K_\mu+K_b)}$, F^* is defined in (36) and A is

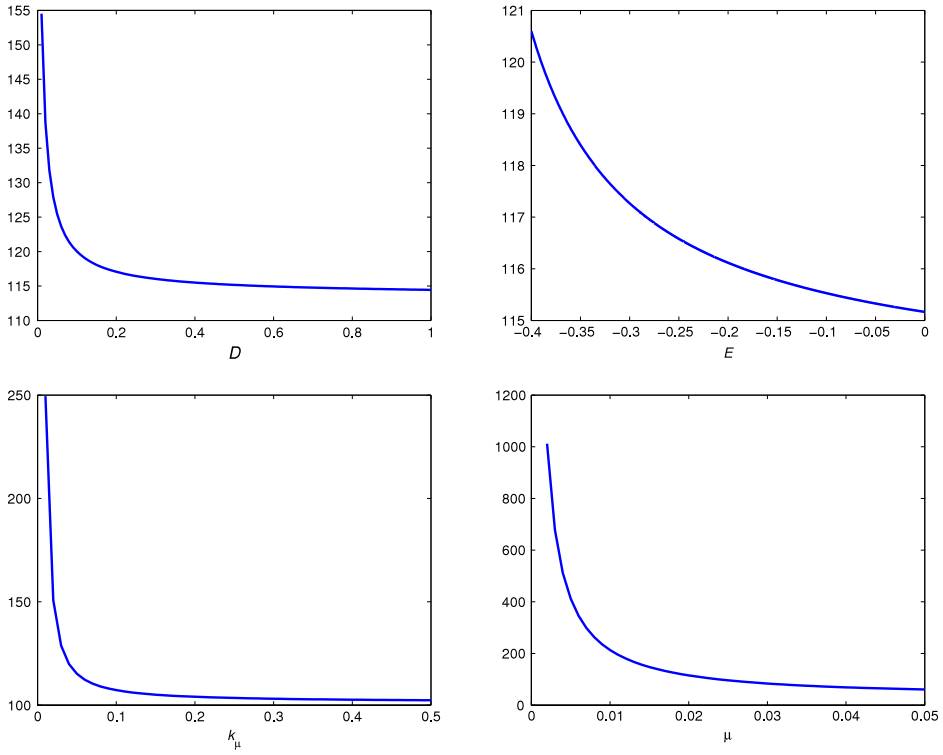

Fig. 3. Behavior of t_{eff}, when t_{eff} is a function of the parameters D, E, K_μ and μ.

Table 2
Predicted and numerical masses for $u_0 = 0.75, v_0 = 0.25, D = 0.6, \gamma = 1, \alpha = 0.2, \mu_1 = \mu_2 = 0.2, E = -0.2, \beta = 1$.

Effective time	Predicted mass (%M_s)	Numerical mass	Relative error
$t_{\text{eff}} = 5.55$	63.21	0.67487895	6.3388×10^{-2}
$2t_{\text{eff}} = 11.11$	86.47	0.88593096	2.3965×10^{-2}
$3t_{\text{eff}} = 16.66$	95.02	0.95982782	1.0031×10^{-2}
$4t_{\text{eff}} = 22.21$	98.17	0.98590559	4.2657×10^{-3}
$5t_{\text{eff}} = 27.76$	99.33	0.99504565	1.7543×10^{-3}

defined in (47). Consequently the Laplace transform of $M(t)$ is given by $\overline{M}(p) = -2\frac{F^*\mu}{p}\left(\frac{u_{\text{ext}}}{p} - S\right)\frac{A\tanh(A\ell)}{AF^*\tanh(A\ell)+\mu}$ and from the Final Value Theorem we obtain a closed formula for the steady mass,

$$M_s = -2\ell\left(u_{\text{ext}}\left(1 + \frac{K_b}{K_\mu}\right) - u_0 - v_0\right). \tag{54}$$

Following (41), we give $\overline{M}(p)$ the form (42). After some tedious but straightforward computations a final expression of t_{eff} is obtained. We do not exhibit this closed form, but just present its plots as a function of D, E, K_μ and μ (Fig. 3). The physical decreasing behavior of effective time with such parameters is observed.

Using (43) and (44) for the mass we have

$$M(Kt_{\text{eff}}) \simeq (1 - \mathrm{e}^{-K})M_s, \quad \forall K \in \mathbb{R}_0^+, \tag{55}$$

with M_s defined in (54). This expression leads to a prediction of the released mass for different values of K.

In what follows we illustrate the use of (55) to estimate the released masses for $f(u, v) = -2u + 2v, g(u, v) = -f(u, v), u_0 = 0.75, v_0 = 0.25$ and $D = 0.6, \gamma = 1, \alpha = 0.2, \mu_1 = \mu_2 = 0.2, E = -0.2, \beta = 1$. We also compare these results with the numerical masses obtained using the numerical method introduced in Section 2.2. The results are presented in Table 2. In Fig. 4 we plot the predicted and numerical masses.

From Table 2 and Fig. 4 we conclude that when K increases the agreement between the prediction and the numerical masses improves.

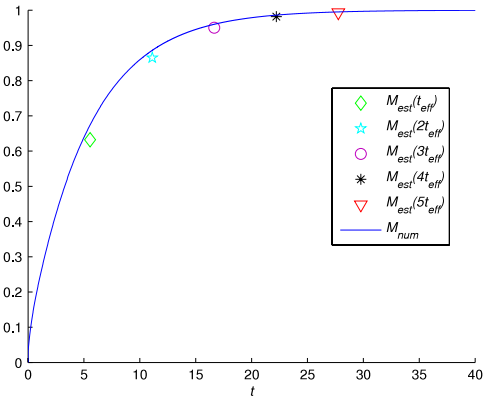

Fig. 4. Predicted (M_{est}) and numerical (M_{num}) masses.

References

[1] R.A. Siegel, Characterization of relaxation to steady state in membranes with binding and reaction, Journal of Membrane Science 251 (2005) 91–99.
[2] J.A. Ferreira, P. de Oliveira, P.M. da Silva, A. Carreira, H. Gil, J.N. Murta, Sustained drug release from contact lenses, Computer Modeling in Engineering and Sciences 60 (2010) 151–180.
[3] R.W. Cox, D.S. Cohen, A mathematical model for stress-driven diffusin in polymers, Journal of Polymer Science Part B: Polymer Physics 27 (1989) 5589–5602.
[4] D.A. Edwards, Constant front speed in weakly diffusive non-Fickian systems, SIAM Journal of Applied Mathematics 55 (1995) 1039–1058.
[5] D.A. Edwards, R.A. Cairncross, Desorption overshoot in polymer-penetrant systems: asymptotic and computational results, SIAM Journal of Applied Mathematics 63 (2002) 98–115.
[6] S. Swaminathan, D.A. Edwards, Traveling waves for anomalous diffusion in polymers, Applied Mathematics Letters 17 (2004) 7–12.
[7] Hal F. Brinson, C. Brinson, Polymer Engineering Science and Viscoelasticity: An Introduction, Springer, NY, 2008.
[8] D.S. Cohen, B. White, Sharp fronts due to diffusion and viscoelastic relaxation in polymers, SIAM Journal of Applied Mathematics 51 (1991) 472–483.
[9] R. Collins, The choice of an effective time constant for diffusive processes in finite systems, Journal of Physics D: Applied Physics 13 (1980) 1935–1947.
[10] Q. Liu, D. De Kee, Modeling of diffusion through polymeric membranes, Rheologica Acta 44 (2005) 287–294.
[11] Q. Liu, X. Wang, D. De Kee, Mass transport through swelling membranes, International Journal of Engineering Science 43 (2005) 1464–1470.
[12] J.A. Ferreira, P. de Oliveira, P. da Silva, L. Simon, Flux tracking in delivery, Applied Mathematical Modelling (2011) doi:10.1016/j.apm.3011.03.035.
[13] A. Araújo, J.A. Ferreira, P. de Oliveira, The effect of memory terms diffusion phenomena, Journal of Computational Mathematics 24 (2006) 91–102.
[14] N. Bauermeister, S. Shaw, Finite-element approximation of non-Fickian polymer diffusion, IMA Journal of Numerical Analysis 30 (2010) 702–730.
[15] J.R. Branco, J.A. Ferreira, P. de Oliveira, Numerical methods for the generalized Fisher–Kolmogorov–Petrovskii–Piskunov equation, Applied Numerical Mathematics 57 (2007) 89–102.
[16] J.R. Branco, J.A. Ferreira, P. da Silva, Non-Fickian delay reaction–diffusion equations: theoretical and numerical study, Applied Numerical Mathematics 60 (2010) 531–549.
[17] J.R. Cannon, Y. Lin, A priori L2 error estimates for finite-element methods for nonlinear diffusion equations with memory, SIAM Journal on Numerical Analysis 27 (1990) 595–607.
[18] J.A. Ferreira, P. de Oliveira, Memory effects and random walks in reaction-transport systems, Applicable Analysis 86 (2007) 99–118.
[19] J.A. Ferreira, P. de Oliveira, Qualitative analysis of a non Fickian model, Applicable Analysis 87 (2008) 873–886.
[20] E.G. Yanik, G. Fairweather, Finite element methods for parabolic and hyperbolic partial integro-differential equations, Nonlinear Analysis: Theory, Methods & Applications 12 (1988) 785–809.
[21] V. Thomée, L.B. Wahlbin, Long-time numerical solution of a parabolic equation with memory, Mathematics of Computation 62 (1994) 477–496.
[22] J. Crank, The Mathematics of Diffusion, Oxford University Press, 1976.
[23] L.W.S. Cheong, P.W.S. Heng, L.F. Wong, Relationship between polymer viscosity and drug release from a matrix system, Pharmaceutical Research 9 (1992) 1510–1514.
[24] S. Cypes, W.M. Saltzman, E.P. Gianneli, Organosilicate polymer drug delivery systems: controlled release and enhanced mechanical properties, Journal of Controlled Release 90 (2003) 163–169.